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PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number (Optional) 03-862-B	
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		First Named Inventor Jeffrey David Bettencourt	
		Art Unit 1654	Examiner M.M. Cordero Garcia
Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a notice of appeal. The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.			
I am the <input type="checkbox"/> applicant/inventor. <input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/98) <input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>35,285</u>		<u>[Signature]</u> Signature <u>Emily Miao</u> Typed or printed name <u>312-913-2126</u> Telephone number <u>May 17, 2007</u> Date	
<input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____			
NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.			
<input checked="" type="checkbox"/> Total of <u>1</u> forms are submitted.			

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(MBHB Case No. 03-862-B)

In re Application of:

Bettencourt et al.

Serial No.: 10/789,246

Filed: February 27, 2004

For: Integrated Capture And Purification
Strategy For Tagged Proteins

Examiner: M.M. Cordero Garcia

Group Art Unit: 1654

Confirmation No. 9463

Mail Stop AF
Commissioner for Patents
Mail Stop 1450
Alexandria, VA 22313-1450**REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Applicant requests review of the Final Office Action mailed December 19, 2006 because the Examiner, when responding to Applicant's arguments, made an error in law.

1. The Claimed Invention

Applicant's claims are directed towards a method for purifying polyhistidine-tagged cytokines from a protein preparation, comprising a negatively charged capture support comprises heparin and a tag-specific affinity support. Claims 1 and 17 recite the various steps for the claimed method and claims 2-5 and 10-11 further define additional elements.

2. Status of the Claims

Claims 1-5, 10-11, and 17 are currently pending. Claims 1 and 17 are independent claims. Claims 1-5, 10-11, and 17 stand rejected on grounds of obviousness over Sporeno (Cytokine, 6(3):255-264 (1994)) in view of Newton (Mol. Biotech. 20:63-76 (2002)).

3. Clear Legal Deficiency of Rejections

In response to Applicant's arguments, the Examiner stated that obtaining a product with less contaminants is a clear motivation to those skilled in the art. Page 3 of the Final Office Action of December 19, 2006. Further, the Examiner acknowledged that although Sporeno does not expressly indicate the desirability of further purification, the Examiner asserted that "there is no hindsight within the motivation to further purify the composition" as "the wisdom in the field recognizes the need for purification." Page 3 of the Final Office Action of December 19, 2006. The Examiner reiterated on page 2 of the Advisory Action dated March 30, 2007 that a desirability to further purify a cytokine exists for many reasons, even if Sporeno is silent with respect to such desirability. Thus, the Examiner concluded that Applicant's invention would be clearly *prima facie* obvious to one of ordinary skill in the art. Page 4 of the Final Office Action of December 19, 2006.

Under *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), the consideration and determination of obviousness under 35 U.S.C. §103 requires the four factual inquiries enunciated therein as a background for determining obviousness. The four factual inquiries are as follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;
- (C) Resolving the level of ordinary skill in the pertinent art; and
- (D) Evaluating evidence of secondary considerations.

However, according to *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007), the Supreme Court has stated a reason to combine references is still necessary, stating:

It can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

In defining a reason to combine, the analysis should be made explicit. See *In re Kahn*, 441 F. 3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

Applicants maintain their previous arguments mentioned in the March 13, 2007 and September 20, 2006 responses, namely that Sporeno does not provide any teaching, motivation or suggestion for removing contaminants before the metal chelating step. Indeed, Sporeno is completely silent for the

need of a heparin column, or for even any further purification using any type of column. Newton adds nothing that remedies the deficiencies in Sporeno because Newton merely relates to purifying a non-cytokine protein using heparin and metal chelating columns. In addition, Sporeno itself does not provide any kind of motivation to combine the teaching of Newton because Sporeno's methods results in a cytokine preparation that is more than 95% pure and fully active, requiring no further purification. See page 256 of Sporeno. Accordingly, one skilled in the art would derive no motivation whatsoever from Sporeno to combine Newton's non-cytokine methods with Sporeno's cytokine methods to arrive at the instant claims for purifying cytokines.

Applicants respectfully submit that the Examiner has failed to establish a case of obviousness. Obviousness rejections cannot be sustained by mere conclusory statements; instead, there must be some explicit and articulated reasoning with rational underpinnings to support the legal conclusion of obviousness. *KSR*, 127 S.Ct. at 1741. Moreover, the test of obviousness under 35 U.S.C. §103 hinges on four factual findings which the Patent Office must follow in determining obviousness. *Graham*, 383 U.S. at 17-18. The Examiner has not identified in Sporeno a desirability or motivation for further purification, and so, the motivation to combine Sporeno with Newton. Indeed, the Examiner has admitted that such desirability does not exist in Sporeno. Page 3 of the Final Office Action of December 19, 2006 and page 2 of the Advisory Action dated March 30, 2007. Thus, Applicant's invention cannot be obvious under the standard engraved in case law.

Furthermore, the Examiner's assertion that Applicant's invention would be obvious to one skilled in the art even if Sporeno lacks a desirability to combine with Newton, implies that the motivation to combine may come from the mind of one skilled in the art. In asserting this position, the Examiner must take the necessary safeguards to prevent hindsight by showing reasons that a skilled artisan, confronted with the same problem as an Applicant and with no knowledge of the Applicant's invention, would select the elements of the references in the manner as Applicant's claims. The Examiner has provided no such explanation. The Examiner failed to explicitly explain how a person skilled in the art would have been motivated to select and combine Sporeno and Newton. Furthermore, there is nothing of record which would lead one skilled in the art to believe that combination of heparin and metal chelating columns to achieve surprisingly high levels of cytokine purification and yields (greater than 99% in both instances) of small amounts of starting material is necessary or desirable to do.

The Supreme Court in *Graham* set out the factual inquiry which the Patent Office must follow in determining obviousness. *Graham*, 383 U.S. at 17-18. The inquiry includes determining the scope and

content of the prior art, ascertaining the differences between the prior art and the claims at issue; resolving the level of ordinary skill in the pertinent art, and evaluating evidence of secondary considerations.

A. Scope and Content of the Cited References

Sporeno is directed to a method for purifying cytokines using a metal chelating column. However, Sporeno does not describe the use of a metal chelating column together with a heparin column for removing contaminants. In fact, Sporeno does not provide any teaching, motivation or suggestion for removing contaminants before the metal chelating step using a heparin column. Newton adds nothing that remedies the deficiencies in Sporeno because Newton merely relates to purifying a non-cytokine protein using heparin and metal chelating columns. In addition, Sporeno itself does not provide any kind of motivation to combine the teaching of Newton because Sporeno's methods results in a cytokine preparation that is more than 95% pure and fully active, requiring no further purification. See page 256 of Sporeno.

B. The Differences Between the Cited References and the Claims

The present claims are directed to a method for purifying polyhistidine-tagged cytokines from a protein preparation, comprising a negatively charged capture support comprises heparin and a tag-specific affinity support. Claims 1 and 17 recite the various steps for the claimed method and claims 2-5 and 10-11 further define additional elements. The claims differ from Sporeno in that Sporeno does not describe a method for purifying cytokines using heparin and metal chelating columns. Sporeno also does not contemplate additional purification steps of any kind, such as a heparin column or any other column together with a metal chelating column for purifying cytokines. As such, Sporeno does not provide any kind of motivation to combine Newton and arrive at the present claimed method for purifying cytokines using heparin and metal chelating columns.

C. Level of Ordinary Skill in the Pertinent Art

Both Sporeno and Newton are of at least ordinary skill in the art, yet the claimed invention did not occur to any one of them. Nothing in either Sporeno or Newton provides a motivation to combine the references to arrive at the claims, namely, method for purifying cytokines using heparin and metal chelating columns. One skilled in the art would derive no motivation whatsoever from Sporeno to

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combine Newton's non-cytokine methods with Sporeno's cytokine methods to arrive at the instant claims for purifying cytokines.

D. Evidence of Secondary Consideration

As demonstrated in Example 1 of the specification, the claimed method is surprisingly useful for purification of minute quantities of human cytokines, providing nearly 100% capture of the polyhistidine-tagged cytokine and greater than 99% final purity as judged by silver stain SDS gels. See, for instance, pages 14 and 15 of the specification.

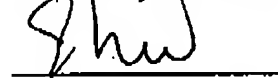
4. Conclusion

Thus, the Applicants submit that under the *Graham* analysis, the present claims are non-obvious in view of Sporeno and Newton and that all of the pending claims should be allowed.

Date:

May 17, 2007

Respectfully submitted,



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